

Internal Medicine

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latest research in internal medicine

[ALERT]

ABSTRACT & COMMENTARY

The Relationship Between Inactivity and Mortality in Heart Failure Patients

By *Harold L. Karpman, MD, FACC, FACP*

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: Physical inactivity in heart failure patients was associated with an increased risk of all-cause death and cardiac death but not with an increased risk of heart failure hospitalization.

SOURCE: Doukky R, Mangla A, Ibrahim Z, et al. Impact of physical inactivity on mortality in patients with heart failure. *Am J Cardiol* 2016;117:1135-1143.

The effect of complete physical inactivity on various cardiovascular outcomes in healthy subjects without heart failure (HF) is well established.¹ However, the effect of physical inactivity on HF patients has been unclear. Researchers previously demonstrated that in subjects without established heart disease, physical inactivity and sedentary time were associated with an increased incidence of new onset HF.^{2,3}

To determine the effect of physical inactivity on mortality in patients with HF, Doukky et al analyzed data from the Heart Failure Adherence and Retention Trial (HART), which was a multihospital, partially blinded, behavioral efficacy, ran-

domized, controlled trial funded by the National Institutes of Health.^{5,6} The study, which enrolled patients from 10 centers in the Chicago metropolitan area, assessed the effect of self-management counseling vs. education alone on the primary outcome of death or HF-related hospitalization in patients with symptomatic HF. No subjects in HART were enrolled in cardiac rehabilitation or other structured exercise training programs. The primary outcome was all-cause death, and the secondary outcomes were cardiac death and HF hospitalization.

The analysis determined that inactive patients were observed to demonstrate a significant increase in

Financial Disclosure: *Internal Medicine Alert's* Editor Stephen Brunton, MD, is a retained consultant for Abbott, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cemptra, Exact Sciences, Janssen, Lilly, Mylan, Novo Nordisk, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Contributing Editor Louis Kuritzky, MD, is a retained consultant for AbbVie, Allergan, AstraZeneca, Janssen, Lilly, Lundbeck, Medscape, Novo Nordisk, and Sanofi Aventis; he serves on the speakers bureau of Lilly and Lundbeck. Peer Reviewer Gerald Roberts, MD; Executive Editor Leslie Coplin; and Associate Managing Editor Jonathan Springston report no financial relationships relevant to this field of study.

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Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, LLC One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850 Atlanta, GA 30326.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Internal Medicine Alert, P.O. Box 550669, Atlanta, GA 30355.

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the risk of all-cause death and cardiac death compared to partially active and fully active subjects and that the risk of all-cause death and cardiac death increased in stepwise patterns with decreasing activity level. However, the difference in the risk of HF hospitalization between groups was not statistically significant.

■ COMMENTARY

The Doukky et al analysis clearly demonstrates that physical inactivity in patients with chronic HF was associated with nearly twice the risk of all-cause death and cardiac death and that even modest leisure exercise was associated with survival benefit. Also interesting was the discovery that television screen time was associated with an incremental risk of all-cause death above and beyond exercise duration and a broad range of sociodemographic and clinical covariates.

A recent cohort study of 82,695 men aged > 45 years of age with no established heart disease demonstrated that sedentary behavior, defined as physical inactivity often associated with significant television viewing screen time, was associated with adverse cardiovascular outcomes.^{7,8}

Doukky et al found that even modest leisure exercise was associated with a significantly reduced risk of all-cause death and cardiac death in patients with chronic HF, regardless of whether the ejection fraction was preserved or reduced. Of course, one must recognize that this study was nonrandomized by design, which slightly or even moderately weakens the final conclusions.

However, the results would certainly suggest that sedentary behavior in patients

with HF is associated with increased risk of all-cause and cardiac death, but not with an increase in HF hospitalizations.

[Clinicians should make every effort to encourage HF patients to exercise routinely and instruct them to avoid excessive periods of inactivity, such as spending too much time in front of the television.]

Clinicians should make every effort to encourage HF patients to exercise routinely and instruct them to avoid excessive periods of inactivity, such as spending too much time in front of the television. ■

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Nature Nurturing Health

By Seema Gupta, MD, MSPH

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Dr. Gupta reports no financial relationships relevant to this field of study.

SYNOPSIS: A national prospective cohort study of nurses found that higher levels of green vegetation were associated with decreased mortality.

SOURCE: James P, Hart JE, Banay RF, Laden F. Exposure to greenness and mortality in a nationwide prospective cohort study of women. *Environ Health Perspect* 2016 Apr 14 [Epub ahead of print].

For the first time in history, a majority of humanity is urbanized, with more than 50% of the planet's 7.1 billion people living in urban areas. As population and urban development increases at an unprecedented rate, it creates a tremendous stress on local, regional, and global air and water quality. Urbanization leads to land use and land cover change, which is a major driver of global environmental change. The growing disease burden in urban areas attributable to nutrition and lifestyle choices remains a major public health challenge. For example, urbanization is associated with profound changes in diet and exercise that in turn increase the prevalence of obesity with attendant increases in risk of type 2 diabetes and cardiovascular disease.¹ Growing evidence suggests close contact with nature benefits health. There is emerging research and policy interest in the potential for using the natural environment to enhance health and well being. Positive health effects of green space have been observed on cardiovascular diseases, mental health, self-reported general health, sleep patterns, and longevity, just to name a few.² Similarly, the use of green space has been associated with higher levels of physical activity and lower levels of obesity within communities.³ Evidence also supports the hypothesis that living in areas with higher amounts of green spaces reduces mortality, mainly related to cardiovascular disease.⁴ However, this evidence is limited in scope, and many studies have relied on aggregated data limiting inferences regarding the effect of greenness on individual health.

James et al used data from the Nurses' Health Study prospective cohort to examine greenness around the homes of 108,630 adult women. Researchers mapped home locations and used high-resolution satellite imagery to determine the level of vegetation within 250 meters and 1,250 meters of the homes. Researchers followed study participants between 2000 and 2008, tracking changes in vegetation and participant deaths. During the study, 8,604 participants died. The authors analyzed models after adjusting for mor-

tality risk factors such as age, race/ethnicity, smoking, and individual- and area-level socioeconomic status. Researchers found that women living in the highest quintile of cumulative average greenness (accounting for changes in residence during follow-up) in the 250 meters area around their homes experienced a 12% lower rate of all-cause, non-accidental mortality (95% confidence interval [CI], 0.82-0.94) compared to those in the lowest quintile. Results remained consistent for the 1,250 meters area, although the relationship was slightly attenuated.

Cause-specific mortality analyses demonstrated that the associations were strongest for respiratory, cancer, and kidney disease mortality. When researchers compared women in the areas with highest greenness to those in the lowest, they found a 34% lower rate of respiratory disease-related mortality (95% CI, 0.52-0.84), a 41% lower rate of kidney disease mortality (95% CI, 0.33-1.05), and a 13% lower rate of cancer mortality (95% CI, 0.78-0.97). Researchers did not note any statistically significant association between greenness and mortality from coronary heart disease, diabetes, or infections.

James et al suggested that a large proportion of the association between greenness and mortality may be explained through mental health pathways of depression risk and social engagement, which subsequently affects mortality.

■ COMMENTARY

Going green could be good for health and society in many ways. This study was the first prospective examination of the relationship between exposure to greenness and mortality across the entire United States, and it demonstrated that nurses who lived in areas with more vegetation experienced lower death rates regardless of age, race/ethnicity, smoking, or socio-economic status. The findings were consistent across all regions of the country (including urban and rural areas) and were most robust for cancer, respi-

ratory, and kidney disease mortality. These findings substantiate previous research in the field.

Biophilia is a theory that suggests an instinctive bond between humans and other living systems; therefore, the theory suggests people have evolved to prefer certain natural environments that are essential to their prospering.⁵ The findings of this study with regard to respiratory and cancer mortality benefits may be attributed to a reduction in air pollution exposure and increased physical activity in the areas of greater greenery. Renal disease mortality benefits also may be related to greater physical activity. Higher exposure to greenness consistently has been linked to lower levels of depression, anxiety, and stress. So it seems that greenness may lower all-cause as well as cause-specific mortality in women, which perhaps can be explained by benefits in mental health, social engagement, physical activity, and lowering of air pollution. If these findings are to be believed, and there is no

reason they should not be, we may find ourselves giving recommendations for planting trees and other vegetation to our patients while saving the environment — something we never learned in medical school. ■

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ABSTRACT & COMMENTARY

The Current Outlook for Cardiac Tamponade

By Michael Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: In the modern era, cardiac tamponade is most commonly caused by malignancies with poor prognosis. As compared to older literature, iatrogenic causes have increased, most resulting from complications of percutaneous coronary intervention.

SOURCE: Sánchez-Enrique C, Nuñez-Gil JJ, Viana-Tejedor A, et al. Cause and long-term outcome of cardiac tamponade. *Am J Cardiol* 2016;117:664-669.

Little is known about the etiologies and prognosis of cardiac tamponade in the modern era. Thus, investigators from Madrid performed a retrospective observational study from 2003 to 2013 on 136 consecutive cases of cardiac tamponade. Patients with large pericardial effusions but no clinical signs of pericardial tamponade were not included. Pericardial fluid was evaluated. An exudative effusion was defined as a pericardial fluid protein to serum protein ratio of > 0.5, fluid that was highly cellular, or had a glucose < 60 mg/dL. The patients were classified into seven groups: infective, neoplastic, uremic, iatrogenic, myocardial infarction (MI), other causes, and idiopathic. Researchers followed all patients for at least 1 year. The median age was 65 years, and 55% were men. Pericardiocentesis was required in 81%. Most had a transudate or hemorrhagic fluid. A positive cytology occurred in 15% and bacteria in 4%. Malignancy was the most common cause (32%), followed by infection (24%), idiopathic (16%), iatrogenic (15%), post-MI (7%), uremic (4%), and other (2%).

The most common malignancies were lung (55%) and breast (18%). In the iatrogenic group, percutaneous coronary interventions (PCI) were the most common. Cardiac tamponade recurred in 10%, and 48% died. Malignancy carried the highest probability of both events (hazard ratio, 5.47; 95% confidence interval, 3.27-9.61; $P < 0.001$). The authors concluded the most common cause of cardiac tamponade is malignancy, and it has the worst prognosis. With aggressive management, other causes have a much better prognosis, especially iatrogenic causes.

■ COMMENTARY

Pericardial tamponade is infrequent, and much of our knowledge about its causes and prognosis is based on older literature. Thus, this contemporary 10-year experience in a modern urban hospital is of interest. Older literature suggested idiopathic was the most common diagnostic category, but now one-third of cases are due to malignancy. There are several possible reasons for this. Physicians may be better at

diagnosing malignant effusions. Before, performing cytology on pericardial fluid was worthless; however, in this series it was positive in 46% of proven malignancy cases. Infection was common, whereas physicians once considered infective cardiac tamponade unusual. Surely the use of polymerase chain reaction and perhaps better culture techniques have increased the ability to diagnose infected fluid. However, the infective causes have changed. Tuberculosis is much less common, although not gone, and the viral causes are now likely to be cytomegalovirus and herpes, rather than coxsackie and echovirus. Although not

in this series, other contemporary populations would have more HIV. Iatrogenic causes would have been unusual in the last century, but now share third place with idiopathic. Interestingly, most of the iatrogenic cases were post-PCI, probably because more stents are deployed now than 10 years ago. Post-MI was next most frequent and it was most commonly free wall rupture. That seems unique to this series, as hospitals with ST elevation MI PCI teams on call rarely experience cardiac rupture. Finally, there were no cases of rheumatic diseases causing tamponade, which may be due to modern therapy with biologic agents. ■

PHARMACOLOGY UPDATE

Daclizumab Injection (Zinbryta)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a humanized monoclonal antibody for the treatment of multiple sclerosis (MS). Daclizumab, which targets the interleukin-2 receptor, is a long-acting injectable drug that is self-administered. It is marketed as Zinbryta.

INDICATION

Daclizumab is indicated for the treatment of adults with a relapsing form of multiple sclerosis (RMS) who have responded inadequately to two or more MS drugs.¹

DOSAGE

The recommended dose is 150 mg administered subcutaneously once monthly. Daclizumab is available as a single-dose prefilled syringe containing 150 mg/mL.

POTENTIAL ADVANTAGES

Daclizumab provides another option, with a different mechanism of action, for the treatment of RMS.

POTENTIAL DISADVANTAGES

Daclizumab can cause severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis.¹ It is contraindicated in patients suffering from pre-existing hepatic disease or hepatic impairment. It also has been associated with other immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis. Immune-mediated disorders occurred in approximately 30% of subjects compared to 12% for interferon-treated subjects.¹

COMMENTS

Daclizumab binds to the alpha subunit of the high-

affinity interleukin-2 receptor and increases signaling through the intermediate-affinity receptor (IL-2R alpha, CXD25).^{1,2} The exact mechanism of action is not clear but is postulated that modulation of IL-2 mediated activation of lymphocytes leads to suppression of MS disease activity. Researchers investigated the efficacy of daclizumab in two randomized, double-blind, controlled studies in patients suffering from RMS.^{1,3,4}

In the first study, subjects experienced at least two relapses during the prior three years and at least one in the prior year, one or more clinical relapses, and one or more new image detected lesions (T1 gadolinium enhanced or T2 hyperintense MRI lesions) within the prior two years or at least one in the prior 12 months. Subjects presenting with progressive forms of MS (Expanded Disability Status Scale [EDSS] > 5) were excluded. Subjects were randomized to 150 mg of daclizumab monthly (n = 919) or 30 mg interferon-beta-1a intramuscularly weekly (n = 922). Annualized relapse rate (ARR) was the primary outcome. Secondary outcomes included the proportion of patients relapsed, the proportion who experienced confirmed disability progression, and the number of newly enlarged T2 hyperdense lesions. At baseline, the mean EDSS was 2.5 (minimum to mild disability) and mean annual relapse was 1.6. ARR up to 144 weeks were 0.216 for daclizumab and 0.393 for interferon-beta-1a, a 45% reduction.^{1,3} The number of new or newly enlarged lesions at 96 weeks was reduced, 4.31 vs. 9.44 (54% reduction). There was no difference in the proportion of confirmed disability progression (16% vs. 20%). Infections, cutaneous events, and elevation of liver enzymes were more common in the daclizumab group.

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The second study included subjects presenting with RMS who experienced at least one relapse in the prior year or who had one or more MRI-detected lesions within six weeks of randomization.^{1,4} Subjects were randomized to daclizumab (n = 208) or placebo (n = 204). Mean EDSS was 2.8 and number relapsed in the prior year was 1.4. ARR at week 52 was 0.211 for daclizumab and 0.458 for placebo (54% reduction). The relative reduction in new lesions was about 70%. Treatment effects were similar for highly active vs. less active patients.⁵ Long-term safety and efficacy are under evaluation in long-term extension studies.^{6,7}

CLINICAL IMPLICATIONS

Currently FDA-approved drugs for the treatment of RMS include self-injected agents (interferon beta-1a, interferon beta-1b, peginterferon beta-1, and glatiramer), oral agents (dimethyl fumarate, fingolimod, and teriflunomide), and intravenous agents (alemtuzumab, mitoxantrone, and natalizumab). Results from a recent network meta-analysis suggest that alemtuzumab, natalizumab, and fingolimod are the most effective for preventing clinical relapse in the first 24 months.⁸ Daclizumab provides another potentially effective treatment of RMS, but because of potential serious adverse events, it is only recommended for patients who inadequately responded to two or more agents. Daclizumab is available through a restricted program under the ZINBRYTA Risk Evaluation and Mitigation Strategy program. Prescribers and pharmacies must

be certified, and patients must enroll in the program. The cost of daclizumab was not available at the time of this review. ■

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CME QUESTIONS

1. Physical inactivity, including television viewing time in subjects presenting with heart failure, has:
 - a. no effect on adverse cardiovascular outcomes.
 - b. been demonstrated to be associated with adverse cardiovascular outcomes.
 - c. no effect on the clinical course.
 - d. None of the above
2. Researchers found that higher levels of green vegetation were associated with lower mortality in all categories *except*:
 - a. respiratory disease.
 - b. renal disease.
 - c. cancer.
 - d. cardiovascular disease.
3. Compared to the last century, the most common cause of pericardial tamponade is:
 - a. malignancy.
 - b. infective.
 - c. iatrogenic.
 - d. uremic.

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Improving Sexual Function and Mood

SOURCE: Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med* 2016;374:7:611-624.

Male hypogonadism is best defined as a clinical syndrome (changes in libido, sexual function, mood, and strength) confirmed by subnormal testosterone. This definition dissuades clinicians from measuring testosterone in asymptomatic men and instituting treatment solely on the basis of low testosterone levels. On one hand, clinical trials of testosterone in asymptomatic men have not demonstrated salutary outcomes. On the other hand, numerous trials confirm improvements in symptoms of hypogonadism through testosterone replacement, albeit with some uncertainty about potential toxicity of testosterone replacement.

Snyder et al performed a double-blind, randomized, placebo-controlled 12-month trial of testosterone replacement (using testosterone gel) in symptomatic hypogonadal men ($n = 790$) ≥ 65 years of age. Testosterone replacement restored testosterone levels to the mid-normal range for young adult men.

Testosterone replacement resulted in statistically significant improvements in sexual function, desire, mood, and depression. Testosterone replacement did not improve walking distance. Testosterone generally was well tolerated, although seven men in the testosterone treatment group developed a hemoglobin > 17.5 mg/dL (none in the placebo group). There was no signal for increased cardiovascular risk, although a much larger trial would be necessary to provide definitive evidence of cardiovascular safety. The authors did not observe any worsening of symptoms relevant to benign prostatic hyperplasia. Testosterone replacement provides several areas of potential symptomatic improvement for hypogonadal men, but ongoing

monitoring for adverse events (such as polycythemia) is necessary. ■

Liraglutide Improves Non-alcoholic Steatohepatitis

SOURCE: Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): A multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679-690.

Hepatosteatosis indicates deposition of fat in the liver in the absence of inflammation. Steatohepatitis is the term for deposition of fat in the liver that is associated with inflammation and fibrosis, which ultimately can lead to end-stage liver disease if untreated. Indeed, it has been suggested that within the next five years, non-alcoholic steatohepatitis (NASH) may become the most common disorder leading to the need for liver transplantation worldwide. As is perhaps implied in the name, the most common NASH etiologies are diabetes and obesity. The prevalence of both continues increasing.

The Liraglutide Efficacy and Action in NASH trial was a double-blind, randomized 48-week study of liraglutide (titrated to 1.8 mg/d subcutaneous) vs. placebo ($n = 52$). All patients were confirmed by biopsy at baseline to have NASH, and were again biopsied at week 48. Specific biopsy-based outcomes included disappearance of hepatocyte ballooning (which indicates resolution of inflammation) without worsening fibrosis, liver function tests, and other hepatic biomarkers. The number of study subjects who attained resolution of NASH was more than four-fold greater in the liraglutide group than placebo (39% vs. 9%).

Liraglutide already is recognized to be a generally safe and well-tolerated medication, including doses up to 3 mg/d subcutaneous in obese patients.

These favorable outcomes should prompt a much larger trial to definitively determine the role of liraglutide in treatment of NASH. ■

Long-acting Anticholinergics and Beta Agonists for COPD

SOURCE: Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD. *Chest* 2016;149:1181-1196.

There has been some suggestion that the bronchodilation afforded by anticholinergic agents, commonly referred to as long-acting antimuscarinic agents (LAMA, e.g., tiotropium, umeclidinium) is at least as good as that provided by long-acting beta-agonists (LABA, e.g., salmeterol, formoterol). Additionally, there does not appear to be any tachyphylaxis associated with LAMA as has been seen with LABA. Since most patients with COPD experience disease progression, pharmacologic augmentation is the rule rather than the exception. Only recently have LAMA/LABA combinations become available. Is LAMA + LABA really better than either alone? And if so, is there a best LAMA/LABA combination?

Calzetta et al performed a systematic review and meta-analysis of controlled trials ($n = 23,168$) that addressed LAMA/LABA combination treatment compared to individual component (LAMA or LABA) monotherapy.

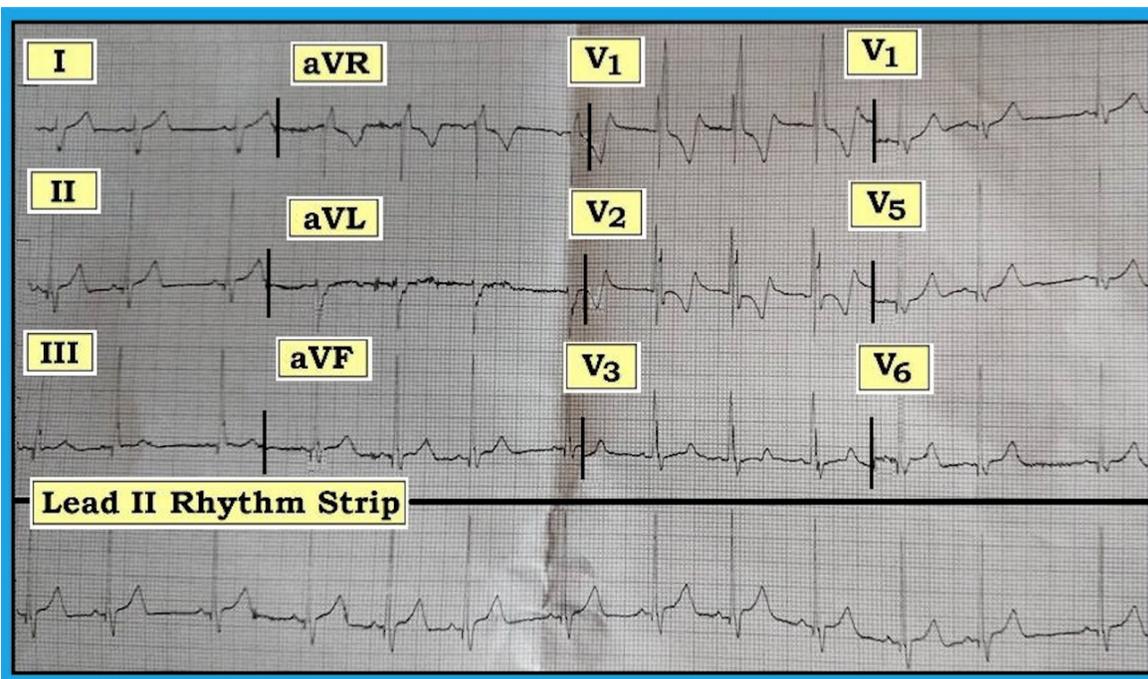
As measured by trough FEV₁, dyspnea indices, and the St. George's Respiratory Questionnaire scores, LAMA/LABA consistently outperformed either monotherapy. Although there are a variety of different LAMA/LABA combinations, no particular combination emerged as distinctly superior. Combining LAMA with LABA provides meaningfully better symptomatic improvement than either agent alone. ■

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Is This ECG Normal for Age?

The ECG in the figure below was obtained from a 6-year-old boy. If no other history was available at the time you were asked to interpret this tracing, what would be your impression?



The mechanism of the rhythm is sinus, as determined by upright P waves with a constant and normal PR interval in the long lead II rhythm strip. The irregularity is the result of marked sinus arrhythmia. The QRS complex is wide (about 0.11 seconds) and manifests a morphology consistent with complete right bundle branch block (RBBB), in that there is an rSR in lead V1, and wide terminal S waves in leads I and V6. Additional findings of interest include the following:

- Left posterior hemiblock (LPHB), suggested by the very steep initial descent to the S wave in lead I in the presence of RBBB.
- Small and narrow Q waves in inferior and lateral leads.
- ST-T wave depression (with a terminal positive T wave component) in leads V1 and V2 that is at least in part secondary to the RBBB, though it seems more pronounced than is usually seen with simple RBBB.
- Some “extra” deflections in the form of terminal S waves in leads II and aVF, and especially the multi-directional QRS complex in lead V2.
- Seemingly generous R wave amplitude in lateral chest leads (24 mm in V5; 20 mm in V6).

Neither sinus arrhythmia nor the small infero-lateral Q waves are abnormal in an asymptomatic child. The seemingly tall lateral chest lead R waves are not outside the normal range for a child this age. On the other hand, complete RBBB is abnormal and of itself would merit further evaluation. Much more than simple RBBB, there is also: 1) LPHB, 2) right ventricular hypertrophy, as suggested by both the markedly increased R amplitude in lead V1 and the right axis deviation, and 3) excessive ST-T wave change in V1, V2, and those extra QRS deflections, both of which are beyond what is expected for simple RBBB. While most primary care providers are not well versed in interpretation of pediatric ECGs, the important point is to recognize that this is not a normal ECG for a 6-year-old child. Significant underlying structural heart disease was suspected. Review of the history revealed that the patient presented with transposition of the great arteries, which a surgeon corrected.

Additional discussion of this case, with a link that reviews the basics of pediatric ECG interpretation, is available at tinyurl.com/KG-Blog-122.